

Food and Drug Administration Silver Spring, MD 20993

Alan Dunbar Executive Director, Regulatory Affairs Amgen, Inc. One Amgen Center Drive Thousand Oaks, CA 91320

RE: BLA #103951

Aranesp[®] (darbepoetin alfa) MA #920

Dear Mr. Dunbar:

The Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed a direct mailer (68899-R1-V1) for Aranesp® (darbepoetin alfa), submitted by Amgen, Inc. (Amgen) under cover of Form FDA-2253. The direct mailer is false or misleading because it omits important risk information associated with the drug, suggests that the drug is useful in a broader range of patients or conditions than has been substantiated, makes unsubstantiated efficacy claims, and omits material facts. Thus, the direct mailer misbrands Aranesp within the meaning of the Federal Food, Drug, and Cosmetic Act (FD&C Act), and makes its distribution violative of the FD&C Act. See 21 U.S.C. 352(a); 321(n); 331(a), and implementing regulation 21 CFR 1.21(a). Cf. 21 CFR 202.1(e)(5)(i), (iii); (e)(6)(i), (x); (e)(7)(i). The direct mailer also provides evidence that Aranesp is intended for a new use for which it lacks approval, and for which its labeling does not provide adequate directions for use, which also renders Aranesp misbranded or otherwise makes its distribution violative. See 21 U.S.C. 355(a); 352(f); 331(a), (d); 21 CFR 201.5; 201.100; 201.115.

Background

Below are the indication and summary of the most serious and common risks associated with the use of Aranesp. According to the INDICATIONS AND USAGE section of the FDA-approved Aranesp product labeling (PI):

- Aranesp is indicated for the treatment of anemia due to chronic kidney disease (CKD), including patients on dialysis and patients not on dialysis.
- Aranesp is indicated for the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy.

Reference ID: 3409569

¹ This information is for background purposes only and does not necessarily represent the risk information that should be included in the promotional piece cited in this letter.

Limitations of Use

Aranesp has not been shown to improve quality of life, fatigue, or patient well-being.

Aranesp is not indicated for use:

- In patients with cancer receiving hormonal agents, biologic products, or radiotherapy, unless also receiving concomitant myelosuppressive chemotherapy.
- In patients with cancer receiving myelosuppressive chemotherapy when the anticipated outcome is cure.
- As a substitute for RBC transfusions in patients who require immediate correction of anemia.

Aranesp is contraindicated in patients with uncontrolled hypertension, pure red cell aplasia (PRCA) that begins after treatment with Aranesp or other erythropoietin protein drugs, and serious allergic reactions to Aranesp.

Aranesp is associated with a number of serious risks. The PI for Aranesp includes a Boxed Warning regarding the increased risk of death, myocardial infarction, stroke, venous thromboembolism, thrombosis of vascular access, and tumor progression or recurrence with the use of erythropoiesis-stimulating agents (ESAs). Because of these risks, prescribers and hospitals must enroll in and comply with the ESA APPRISE Oncology Program to prescribe and/or dispense Aranesp.

The PI for Aranesp contains Warnings and Precautions regarding increased mortality and/or risk of tumor progression or recurrence in patients with cancer; hypertension; seizures; lack or loss of hemoglobin (Hb) response to Aranesp; pure red cell aplasia; serious allergic reactions; dialysis management; and laboratory monitoring. The most common adverse reactions in patients with chronic kidney disease receiving Aranesp were hypertension, dyspnea, peripheral edema, cough, and procedural hypotension. The most common adverse reactions in cancer patients receiving chemotherapy were abdominal pain, edema and thrombovascular events.

Omission of Risk Information

Promotional materials are misleading if they fail to reveal facts that are material in light of representations made or with respect to consequences that may result from the use of the drug as recommended or suggested by the materials.

Page two of the direct mailer includes a presentation of the Boxed Warning and some risk information for Aranesp, but fails to disclose the following material facts from the WARNINGS AND PRECAUTIONS section of the Aranesp PI:

• 5.1 Increased Mortality, Myocardial Infarction, Stroke, and Thromboembolism

"In controlled clinical trials, ESAs increased the risk of death in patients undergoing coronary artery bypass graft surgery (CABG) and the risk of deep venous thrombosis (DVT) in patients undergoing orthopedic procedures."

• 5.6 Lack or Loss of Hemoglobin Response to Aranesp

"For lack or loss of hemoglobin response to Aranesp, initiate a search for causative factors (e.g., iron deficiency, infection, inflammation, bleeding). If typical causes of lack or loss of hemoglobin response are excluded, evaluate for PRCA."

5.7 Pure Red Cell Aplasia

"Cases of PRCA and of severe anemia, with or without other cytopenias that arise following the development of neutralizing antibodies to erythropoietin have been reported in patients treated with Aranesp. This has been reported predominantly in patients with CKD receiving ESAs by subcutaneous administration. PRCA has also been reported in patients receiving ESAs for anemia related to hepatitis C treatment (an indication for which Aranesp is not approved).

. . .

Permanently discontinue Aranesp in patients who develop PRCA following treatment with Aranesp or other erythropoietin protein drugs. Do not switch patients to other ESAs."

The omission of this important risk information regarding multiple Warnings and Precautions for Aranesp misleadingly suggests that the drug is safer than has been demonstrated. We acknowledge that the direct mailer includes the statements, "Please see accompanying Aranesp[®] full prescribing information, including **Boxed WARNINGS** and Medication Guide" as well as "Visit Aranesp.com for more information," however, these statements do not mitigate the misleading omission of important risk information from the direct mailer.

Broadening of Patient Population or Condition

Promotional materials are misleading if they suggest that a drug product is useful in a broader range of conditions or patients than has been demonstrated by substantial evidence or substantial clinical experience.

The direct mailer presents the following claims and presentations:

- "For chemotherapy-induced anemia (CIA) in metastatic patients with Hb<10 g/dL" (page 1)
- "Catch hemoglobin levels before they fall too far," presented in conjunction with an image of a man, composed of red blood cells, in a free-fall (page 1)
- "Stabilize the fall" (page 3)

The totality of these claims and presentations misleadingly suggests that Aranesp is useful to treat chemotherapy-induced anemia in any patient with metastatic cancer whose hemoglobin

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is falling, or has fallen below 10g/dL, when this has not been demonstrated by substantial evidence or substantial clinical experience. As described above, Aranesp's approved indication is limited to the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy. Moreover, Aranesp is not indicated for use in patients with cancer receiving hormonal agents, biologic products, or radiotherapy, unless also receiving concomitant myelosuppressive chemotherapy; in patients with cancer receiving myelosuppressive chemotherapy when the anticipated outcome is cure; or as a substitute for RBC transfusions in patients who require immediate correction of anemia. Information sufficient to support use in the broader patient population or condition suggested in this direct mailer has not been submitted to FDA in an application, nor are we otherwise aware of substantial evidence or substantial clinical experience that would support it. We acknowledge that the approved indication is included on page three of the direct mailer. However, this information does not mitigate the overwhelming impression that Aranesp is useful in a much broader range of patients than has been demonstrated by substantial evidence or substantial clinical experience. These claims in the direct mailer also provide evidence that Aranesp is intended for a new use for which it lacks approval, and for which its labeling does not provide adequate directions for use.

Unsubstantiated Efficacy Claims

Promotional materials are misleading if they contain a representation or suggestion that a drug is more effective than has been demonstrated by substantial evidence or substantial clinical experience.

Page three of the direct mailer includes the headline, "Reduce RBC transfusions and achieve a **gradual and steady** Hb rise with Aranesp^{®2,3,4}" (emphasis added), and cites references in support of this claim. This claim suggests that patients taking Aranesp will experience a consistent, controlled rise in hemoglobin (Hb), when this has not been demonstrated by substantial evidence or substantial clinical experience. The references used to support this claim consist of two publications, outlining each of the pivotal studies used for approval of Aranesp for the treatment of chemotherapy-induced anemia, as well as the Aranesp PI. However, these references do not provide substantial evidence to support the claim. The rate of Hb rise was not an endpoint in any of the clinical studies. In contrast to the claim, the Aranesp PI includes individualized dosage adjustment recommendations based on patient response, using the lowest dose of Aranesp necessary to avoid RBC transfusions. For example, the DOSAGE AND ADMINISTRATION section of the Aranesp PI states that dosage reductions of 40% are recommended if hemoglobin levels increase greater than 1 g/dL in any 2-week period. In light of this information, it is misleading to claim that Aranesp provides a "gradual and steady" rise in Hb.

² Aranesp[®] (darbepoetin alfa) Prescribing Information, Amgen.

³ Vansteenkiste J, Pirker R, Massuti B, et al. Double-Blind, Placebo-Controlled, Randomized Phase III Trial of Darbepoetin Alfa in Lung Cancer Patients Receiving Chemotherapy. Journal of the National Cancer Institute.

Canon JL, Vansteenkiste J, Bodoky G, et al. Randomized, Double-Blind, Active-Controlled Trial of Every-3-Week Darbepoetin Alfa for the Treatment of Chemotherapy-Induced Anemia. Journal of the National Cancer Institute. 2006;98:273-284.

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Page three of the direct mailer presents the claim, "In untreated patients whose Hb fell below 10 g/dL, 1 in 3 required an RBC transfusion within 6 weeks⁵" in conjunction with the claim. "Aranesp® significantly reduced the need for RBC transfusions by 48% compared to placebo." The totality of this presentation suggests that Aranesp can reduce the proportion of patients requiring RBC transfusion by 48%, from 1 in 3 (~33%) to approximately 1 in 6 (~17%), which is not the case. According to the CLINICAL STUDIES section of the PI, in Study C1⁶, the crude percentage of Aranesp-treated patients requiring a RBC transfusion was 26%, which is considerably higher than the ~17% suggested by the presentation of these two claims together. Moreover, the claim that 1 in 3 untreated patients required a RBC transfusion is not supported by substantial evidence or substantial clinical experience. The reference cited for this claim describes a post-hoc, exploratory, pooled analysis of placebotreated patients from six separate clinical trials. Retrospective evaluation of outcomes from a pooled population of different patients across various studies does not constitute substantial evidence or substantial clinical experience to support efficacy claims for Aranesp. Thus, the totality of this presentation misleadingly implies a more significant reduction in RBC transfusion requirements than has been demonstrated by substantial evidence or substantial clinical experience.

Omission of Material Fact

Promotional materials are misleading if they fail to reveal facts that are material in light of the representations made by the materials or with respect to consequences that may result from the use of the drug as recommended or suggested in the materials. The direct mailer claims that "Aranesp® can be synchronized with the majority of chemotherapy regimens, including Q3W7." This claim indicates that Aranesp can be administered every three weeks, which is consistent with the approved instructions, but the piece fails to provide ANY other information regarding the approved dosing of Aranesp. The PI for Aranesp provides extensive instructions that are material for dosing Aranesp, including the starting dose, several different dosing schedules, laboratory monitoring requirements, and instructions for subsequent dose adjustments in response to fluctuations in Hb levels during treatment. Without any of this important dosing information, the direct mailer fails to provide the information necessary for healthcare practitioners to determine how to appropriately dose Aranesp so as to synchronize it with their patients' chemotherapy regimens, as the piece suggests.

Conclusion and Requested Action

For the reasons discussed above, this direct mailer misbrands Aranesp within the meaning of the FD&C Act, and makes its distribution violative. See 21 U.S.C. 352(a); 321(n); 331(a), and implementing regulation 21 CFR 1.21(a). Cf. 21 CFR 202.1(e)(5)(i), (iii); (e)(6)(i), (x); (e)(7)(i). The direct mailer also provides evidence that Aranesp is intended for a new use for which it lacks approval, and for which its labeling does not provide adequate directions for use, which

⁵ Pirker R, Collins H, Legg J, et al. *Journal of Clinical Oncology 2011 ASCO Annual Meeting Proceedings (Post-Meeting Edition)*. Vol 29, No 15 suppl (May 20 supplement), 2011: Abstract e19637.

⁷ Data on File, Amgen; [Tandem Anti-cancer and Tumor Audit].

⁶ Study C1 was a randomized, placebo-controlled, double-blind, study conducted in 314 anemic patients (hemoglobin ≤ 11 g/dL) with non-small cell lung cancer or small cell lung cancer who were scheduled to receive at least 12 weeks of a platinum-containing chemotherapy regimen. Aranesp was administered weekly.

also renders Aranesp misbranded or otherwise makes its distribution violative. See 21 U.S.C. 355(a); 352(f); 331(a), (d); 21 CFR 201.5; 201.100; 201.115.

OPDP requests that Amgen immediately cease misbranding Aranesp. Please submit a written response to this letter on or before December 4, 2013, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Aranesp that contain statements such as those described above, and explaining your plan for discontinuing use of such materials.

Please direct your response to the undersigned at the Food and Drug Administration, Center for Drug Evaluation and Research, Office of Prescription Drug Promotion, 5901-B Ammendale Road, Beltsville, Maryland 20705-1266 or by facsimile at (301) 847-8444. To ensure timely delivery of your submissions, please use the full address above and include a prominent directional notation (e.g. a sticker) to indicate that the submission is intended for OPDP. Please refer to MA # 920 in addition to the BLA number in all future correspondence relating to this particular matter. All correspondence should include a subject line that clearly identifies the submission as a "Response to Untitled Letter." OPDP reminds you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your distribution of Aranesp complies with each applicable requirement of the FD&C Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

James S. Dvorsky, PharmD Regulatory Review Officer Office of Prescription Drug Promotion

{See appended electronic signature page}

Karen Rulli, Ph.D.
Team Leader
Office of Prescription Drug Promotion

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JAMES S DVORSKY
11/19/2013

KAREN R RULLI 11/19/2013